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Original Article

Observational study to evaluate the safety and efficacy of saroglitazar in Indian diabetic dyslipidemia patients

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ABSTRACT

Saroglitazar is a dual PPAR α/γ agonist approved in India for the management of diabetic dyslipidemia.

Aims: The objective of this study was to evaluate the safety and efficacy of saroglitazar 4 mg once daily in clinical practice.

Methods: This was an observational, multicenter, single-arm study. Patients with type 2 diabetes (with on-going antidiabetic medication), age above 18 years, and triglycerides $\geq$200 mg/dL were included.

Results: A total 2804 patients with a mean duration of diabetes 6.29 yrs were included in this analysis. The baseline demographic profile was: mean age of 53 yrs, mean body weight 72.3 kg and mean BMI of 27 kg/m^2. 62.5% patients were male and 57.8% were reported to be on statin therapy at baseline. All 2804 patients were on antidiabetic medications with 15.4% patients on monotherapy and rest were on two or more than two antidiabetic medications at baseline. The baseline triglycerides and HbA1C values were 312.3 mg/dL and 8.3% respectively. At 3 months follow-up, use of saroglitazar 4 mg led to significant reduction in TG (35.8%), LDL-C (16.4%), total cholesterol (19%) and non-HDL-C (23.4%). Addition of saroglitazar to baseline antidiabetic medications showed a significant 0.9% absolute reduction in HbA1c with significant improvement in fasting and post prandial plasma glucose. No serious adverse events, alteration in liver or renal enzymes and edema or weight gain were reported.

Conclusion: Saroglitazar is a potential therapeutic option in type 2 diabetic patients with high TG levels, not controlled by statins, for comprehensive control of lipid and glycemic parameters with acceptable safety profile.

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1. Introduction

The cardiovascular diseases (CVDs) burden globally and as well in India is rising sharply and presently is the number one cause of mortality.[1] INTERHEART study, a major Canadian-led global study identified 9 easily measured risk factors (smoking, lipids, hypertension, diabetes, obesity, diet, physical activity, alcohol consumption, and psychosocial factors) that account for over 90% of the risk of acute myocardial infarction (AMI) and dyslipidemia being the strongest risk predictor globally.[2] Diabetic dyslipidemia (DD) is an important factor contributing to the increased risk of CVDs.[3] Studies have shown that three out of four diabetes patients globally have associated dyslipidemia.[4] DD, also known as atherogenic dyslipidemia, is the triad of high triglycerides (TG), higher proportion of small dense low density lipoprotein cholesterol (sd-LDL-C) and low high density lipoprotein cholesterol (HDL-C).[5] Currently statins, fibrates, niacin and omega 3 fatty acids are the available drugs in the armamentarium for the treatment of dyslipidemia. Saroglitazar is the novel molecule approved in India for the management of DD. It is the first dual peroxisome proliferator activated receptor (PPAR)-α/γ agonist to have successfully completed its clinical research and to be approved for clinical use anywhere in the world. In previous studies, saroglitazar has shown significant benefit in terms of improvement in lipid and glycemic parameters with good safety profile. There has been a 46.7% decrease in TG, 32.5% decrease in non-HDL-C, 0.3% absolute reduction in glycosylated hemoglobin (HbA1c) with saroglitazar 4 mg in Indian DD patients.[6,7] The present observational study was done to evaluate the safety and efficacy of saroglitazar in Indian DD patients in clinical practice.

2. Methodology

This was an observational, multicenter, single-arm, post marketing study of saroglitazar 4 mg in Indian DD patients (at outpatient clinic settings) who were prescribed saroglitazar 4 mg once daily as per the approved indication (diabetic dyslipidemia and hypertriglyceridemia in type 2 diabetes not controlled with statin). Only patients who qualified for saroglitazar treatment as per treating physician's clinical judgment (as per prescribing information of saroglitazar) in outpatient settings were included in this analysis. There was no experimental intervention done. Patients with type 2 diabetes (with on-going antidiabetic medication), age above 18 years and triglycerides $\geq$200 mg/dL were included. The exclusion criteria were pregnancy, lactating mothers, active liver disease, NYHA class III or IV heart failure, malignancy, or patients with history of hypersensitivity to saroglitazar or any of the excipients used in the formulation. The data were collected from the treating physicians who had prescribed saroglitazar between November 2013 and July 2014. In this observational analysis, 3133 patient data were obtained and only those with antidiabetic medications recorded at baseline were included in the final analysis. Antidiabetic medications at baseline were not reported in 329 patients, hence 2804 patient data were considered. All these 2804 patients were prescribed tablet saroglitazar 4 mg once daily before breakfast. Baseline and 3 month glycemic parameters (HbA1c, Fasting plasma glucose, post-prandial plasma glucose), lipid parameters (total cholesterol, LDL-C, HDL-C, TG, non-HDL-C) and adverse event if any reported were recorded. The laboratory tests were conducted at centers recommended by treating physicians. The LDL-C values are direct, not calculated from Friedewald equation. Non-HDL-C was calculated by subtracting HDL-C value from total cholesterol value. Only those patient data which had both baseline and 3 month follow up data were considered for individual laboratory parameters analysis (e.g. in Table 4, for the analysis of effect on TG, out of the total 2804 patient data, 2767 were used for analysis as they had both baseline and 3 month follow up TG values recorded). The SAS® system for Windows (release 9.3; SAS Institute) was used for statistical analysis. Significant differences in the means from baseline to post baseline were assessed by paired *t*-tests. "*p*" value of <0.05 was considered as significant.

3. Results

The data of 3133 patients prescribed saroglitazar 4 mg once daily was recorded at baseline and at 3 months and analyzed. All were type 2 diabetes patients with average duration of diabetes of 6.29 years. The mean age of the patients was 53 years and 62.5% of the patients were male. The patients had a mean weight of 72.3 kgs and a mean body mass index of 27.0 kg/m^2 (Table 1). Out of 3133 patients, 284 were reported to have history of coronary heart disease.

In this study 57.8% of patients were reported to be on statin therapy, with atorvastatin being the most commonly used statin (69.6%), at the time of entry (Table 2). All patients were advised to continue on-going statin therapy and saroglitazar 4 mg once daily was prescribed as 2nd line lipid-lowering agent.

Out of 3133 patients, concomitant antidiabetic medications at baseline were recorded in 2804 patients (89.5%) and only these patient data were utilized for further analysis. Saroglitazar 4 mg was prescribed in addition to on-going single antidiabetic therapy in 15.4%, to on-going dual antidiabetic therapy in 43.4% and in addition to more than two on-going antidiabetic therapy in 41% of the patients (Table 3a and b). In the study population (n = 2804), the most commonly reported antidiabetic drug at baseline was metformin in 79.3% of the patients, followed by sulphonylureas in 60.2%, gliptins in 31.1%, alpha glucosidase inhibitors in 18.90%, insulin in 14.7%, thiazolidinediones in 6.5%, meglitinide analogs in 0.9%, GLP 1 agonist 0.2% and bromocriptine in <1% (Table 3c).

Table 1 – Demographic profile of patients (N = 3133).

Age (years); n = 3100	53 ± 10
Male	1958 (62.5%)
Weight (kg); n = 2737	72.3 ± 11.45
BMI (kg/m^2); n = 2565	27.0 ± 4.17
Average duration of diabetes (years); n = 2562	6.29 ± 6.20

Data are mean ± SD values or number (%) as indicated. **Abbreviations**: N = number of subjects in specified treatment; n = number of subjects at specified category; BMI = body mass index. Data Determined at baseline.

Table 2 – Number of patients (%) with or without on-going statin therapy at baseline (N = 3133).

With statin	1812 (57.8%)
Atorvastatin	1262 (69.6%)
Rosuvastatin	543 (30.0%)
Pitavastatin	4 (0.2%)
Simvastatin	2 (0.1%)
Pravastatin	1 (0.1%)
Without statin	**1321 (42.2%)**

Saroglitazar in addition to oral antidiabetic medication showed significant improvement in all lipid and glycemic parameters at 3 month follow-up. The mean baseline TG was 312.3 mg/dL vs. 188.7 mg/dL at 3 month follow-up, a significant reduction of 35.8% (mean of % change from baseline). Non-HDL-C levels also reported a significant 23.4% mean reduction at 3 month follow-up. A statistically significant improvement in all other lipid parameters was also noted (a mean reduction of 16.4% in LDL-C levels, 31.5% in VLDL-C levels, 19% in total cholesterol levels and mean increase of 7.3% in HDL-C levels).

Analysis of glycemic parameters revealed a statistically significant 0.9% absolute reduction in HbA1c from baseline value of 8.3% to 7.4% at 3 month follow-up. A significant reduction in fasting plasma glucose level of 23.6% from a mean baseline of 175.2 mg/dL to mean follow-up value of 128.9 mg/dL and a significant 26.3% mean reduction in post-prandial plasma glucose level from mean baseline level of 262.4 mg/dL to mean follow-up value of 185.2 mg/dL were observed (Table 4).

Saroglitazar administration did not lead to weight gain. The mean body weight at baseline was 72.3 kgs and at 3 month follow-up was 71.6 kgs. No serious adverse events were reported.

4. Discussion

Statins are recommended as the primary therapy for the management of dyslipidemia in diabetes by various guidelines like the 2013 American Heart Association and the 2015 American Diabetic Association guidelines for the management of dyslipidemia.[8,9] Residual cardiovascular risk remains a major concern after statin therapy and atherogenic diabetic dyslipidemia is postulated to be a major factor. Studies have shown that in comparison to Caucasians, Indians have higher TG levels and an associated low HDL-C.[10,11] High TG has been long debated to be a major risk factor for CVD and today there is growing evidence which associating higher TG levels with increased CVD disease. A recent observational study in more than 75,000 subjects from general population, followed up for 34 years has revealed that lower TG level was associated with lower CV risk. It was observed that the group with TG <90 mg/dL had 60% lower risk (statistically significant) of ischemic heart diseases than those with TG ≥360 mg/dL.[12] Another metaanalysis published in 2014 revealed that non-fasting TG of 600 mg/dL versus 72 mg/dL was associated with hazard ratio of 5.1 (95% CI 3.5–7.2) for myocardial infarction, 3.2 (2.5–4.1) for ischemic heart disease, 3.2 (2.2–4.7) for ischemic stroke, and 2.2 (1.8–2.7) for all-cause mortality.[13] Thus, higher TG level is found to be associated with increased cardiovascular risk. The latest American Association of Clinical Endocrinology (AACE) dyslipidemia guidelines also recommend a non-HDL-C calculation rather than LDL-C calculation alone when TG is above 200 mg/dL but <500 mg/dL for better risk assessment especially in insulin resistance.[14] The AACE diabetes guidelines suggest that non-HDL-C goal is to be achieved with TG lowering therapy after achievement of desirable LDL-C level.[15] The European Society of Cardiology 2011 dyslipidemia guidelines recommend TG lowering with drugs to be considered in subjects with TG more than 2.3 mmol/L (more than 200 mg/dL) who cannot lower them by lifestyle measures.[16] Metaanalysis of the five major fibrate trials has shown 35% statistically significant decrease in coronary heart disease with fibrates in the group with baseline TG ≥204 mg/dL and HDL-C ≤34 mg/dL.[17] Thus there is increasing evidences bolstered by guidelines supporting the control of TG to manage non-HDL-C and cardiovascular risk. Unfortunately, the currently available options for the treatment of high TG, fibrates and niacin, are associated with several side effects which limits their use. The use of fibrates is associated with higher risk of muscle symptoms when given in conjunction with statins, increased risk of choleolithiasis, and alteration in renal and liver parameters.[18] Niacin is associated with decreased patient compliance due to skin flushes, and also manifests glucose intolerance.[19] In this context, saroglitazar, a novel molecule, is a dual PPAR-α/γ agonist, approved for the use of DD. The present study shows that saroglitazar in addition to statins led to a significant improvement in lipid parameters. At 3 month there was a significant reduction in TG of 35.8%, LDL-C of 16.4%, total cholesterol of 19% and non-HDL-C of 23.4%. Further, in patients (with average duration of diabetes of 6.29 years) on existing baseline antidiabetic medications, the addition of saroglitazar, showed a significant 0.9% absolute reduction in HbA1c and significant improvement in fasting and post prandial plasma glucose. Finally, there were no serious adverse events or alteration in liver or renal enzymes and edema or weight gain reported in this study.

Table 3 – Pattern of baseline antidiabetic therapy.

a. Number of patients (%) with or without on-going antidiabetic therapy (N = 3133)	
Patients with antidiabetic therapy	2804 (89.5%)
Patients without antidiabetic therapy	329 (10.5%)
b. Number of patients (%) with single, dual or more than two antidiabetic drugs (*n* = 2804)	
Single antidiabetic drug	433 (15.4%)
Dual antidiabetic drug	1218 (43.4%)
More than two antidiabetic drugs	1153 (41.1%)
c. Pattern of antidiabetic drug; (*n* = 2804)	
Metformin	2486 (79.3%)
Sulphonylureas	1886 (60.2%)
Gliptins	973 (31.1%)
Alpha glucosidase inhibitors	529 (18.90%)
Insulin	460 (14.7%)
Thiazolidinediones	205 (6.5%)
Meglitinide analogs	29 (0.9%)
GLP 1 agonist	6 (0.2%)
Bromocriptine	1 (0.0%)

*Data as number of patients (%).

Table 4 – Change in lipid and glycemic parameters after 3 months treatment with saroglitazar 4 mg once daily (N = 2804).

Laboratory parameter	Baseline	3-month follow up	Absolute change	Percentage change (%)
TG (mg/dL); *n* = 2767	312.3 ± 122.65	188.7 ± 61.40	−123.7 ± 104.39*	−35.8 ± 19.34
LDL-C (mg/dL); *n* = 2694	139.5 ± 42.16	112.4 ± 30.83	−27.1 ± 30.06*	−16.4 ± 23.94
HDL-C (mg/dL); *n* = 2453	38.8 ± 8.65	41.0 ± 7.14	2.1 ± 5.92*	7.3 ± 15.08
VLDL-C (mg/dL); *n* = 2070	52.0 ± 9.95	34.8 ± 9.07	−17.1 ± 10.64*	−31.5 ± 18.29
Total cholesterol (mg/dL); *n* = 2388	240.2 ± 63.04	189.9 ± 41.29	−50.3 ± 46.24*	−19.0 ± 14.34
Non-HDL-C (mg/dL); *n* = 2265	201.8 ± 64.08	149.4 ± 41.02	−52.3 ± 46.93*	−23.4 ± 16.89
HbA1c (%); *n* = 2612	8.3 ± 1.28	7.4 ± 0.89	−0.9 ± 0.85*	–
Fasting plasma glucose (mg/dL); *n* = 2549	175.2 ± 53.34	128.9 ± 33.17	−46.3 ± 42.95*	−23.6 ± 16.59
Post-prandial plasma glucose (mg/dL); *n* = 2295	262.4 ± 80.26	185.2 ± 48.25	−77.1 ± 65.14*	−26.3 ± 17.58

All values in Mean ± SD. Abbreviations: N = number of subjects in specified treatment; *n* = number of subjects having non-missing values at baseline and post-baseline visits. *p*-values are calculated from paired *t* - test. **p* value <0.0001.

5. Limitations of the study

This is not a randomized, controlled clinical trial and this analysis consist of data obtained from real time clinical practice. The data were analyzed at a short duration of 3 month follow up. Adherence to therapy could not be assessed in this analysis. Laboratory tests were not conducted at specific assigned laboratory. More randomized, controlled clinical trials with longer duration of follow up will be necessary.

6. Conclusions

In patients with diabetic dyslipidemia, the use of saroglitazar 4 mg once daily for 3 month is associated with significant improvement of lipid and glycemic parameters. Saroglitazar was safe, well tolerated and there was no serious adverse event reported.

Conflicts of interest

Dr Ashok D Jaiswal is an employee of Cadila Healthcare, Ahmedabad.

All authors have none to declare.

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